PATENT COOPERATION TREATY

PCT

REC'D 28 AUG 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2026-4308PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15293	02/06/2000	04/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/51		
Applicant THE GOVERNMENT OF THE U.S.A. ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/01/2001	24.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mundel, C Telephone No. +49 89 2399 7314

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/15293

I. Basis of th report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-35, filed with the letter of 07.07.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-38
	No:	Claims	1-2, 4, 6-13, 15-17 and 39-40 & 3, 5, 14, 18 (see Citations and explanations)
Inventive step (IS)	Yes:	Claims	19-38
	No:	Claims	1-18 and 39-40
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re It m II
Priority

The priority document of the present application was not available at the time where thisInternational Preliminary Examination Report (IPER) has been drafted. The present analysis is based on the hypothesis that all the claims have a priority right corresponding to the date of filing of the priority document (04.06.99).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statem nt

1. The present application refers to an isolated nucleic acid molecule encoding an infectious GB virus-B, to cells transfected with said nucleic acid, to GB virus-B polypeptides and to GB virus-B. The application also refers to methods for producing GB virus-B and to compositions comprising an isolated nucleic acid molecule encoding an infectious GB virus-B. The application also refers to chimeric virus genomes comprising GB virus-B nucleic sequences and hepatitis C virus sequences, to viruses comprising such genomes and to polypeptide encoded by said chimeric virus genomes.

2. **Reference is made to the following documents :**

   D1: WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17).

   D2: YANAGI MASAYUKI ET AL: 'In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, cited in the application.

   D3: SCARSELLI ELISA ET AL: 'GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity.' JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, cited in the application.

   D4: KOLYKHALOV A. A. et al.: "Identification of a highly conserved sequence element at the 3' terminus of hepatitis C virus genome RNA". Journal of

virology, vol. 70, No. 6, June 1996, pages 3363-3371.

D5: HONDA MASAO ET AL: 'A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation.' JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, cited in the application.

The document D4 was not cited in the international search report.

3. Lack of novelty; article 33(2) PCT.

3.1 The document D1 discloses hepatitis GB virus (HGBV) nucleic acid and amino acid sequences useful for a variety of diagnostic and therapeutic applications (Abstract). D1 claims a recombinant polynucleotide characterized by a positive stranded RNA genome wherein said genome comprises an open reading frame encoding a polyprotein having at least 35% identity and more preferably 80% identity to an amino acid sequence selected from the group consisting of HGBV-A, HGBV-B and HGBV-C (p. 4, lines 19-27). Moreover D1 refers to a **recombinant vector comprising said polynucleotide** and to **host cells** transformed with said vector (p. 5, lines 1-4). Cells which will be suitable for culturing HGBV are also disclosed (p. 55, line 25 to p. 56, line 19). Example 9 of D1 discloses the "complete" sequence of the HGBV-B genome (SEQ ID NO:393) and the corresponding amino acid sequence (SEQ ID NO: 396 and 397).

The IPEA considers that the nucleic acid sequence disclosed in SEQ ID NO:393 can be considered as encoding a GB virus-B and that said nucleic acid would be capable of expressing said virus when transfected into cells. Moreover, said nucleic acid molecule can be considered as encoding the amino acid sequence of SEQ ID NO:2. Therefore, claim 1-2, 4, 6-13 and 15-17 can not be considered as novel in the sense of article 33(2) PCT.

Moreover, the attention of the applicant is drawn to the fact that even if the 3' sequence disclosed in the present application has not been disclosed in D1, at least some of the HGBV-B viruses used in D1 - being infectious - had said

3' terminal sequence. Therefore, even the novelty of claims 3, 5, 14 and 18 is questionable.

3.2 Claims 39 and 40 of the present application refer to a polypeptide encoded by the nucleic acid molecule of claims 19, 24 or 27. The attention of the applicant is drawn to the fact that the sequence of the polyprotein encoded by the GB virus-B was well-known from the document D1. Moreover, the scope of claims 39 and 40 also encompasses well-known hepatitis C virus proteins. Therefore, claims 39 and 40 lack novelty in the sense of article 33(2) PCT.

3.3 The subject-matter of claims 19-38 has never been disclosed in the documents cited in the International Search Report (ISR). Therefore, claims 19-38 are considered as novel in the sense of article 33(2) PCT.

4. Lack of inventive step; article 33(3) PCT.

4.1 The document D2 has been considered as the most relevant document for the evaluation of the inventiveness of the claims.
D2 discloses the in vivo analysis of the **3' untranslated region of the hepatitis C virus** after in vitro mutagenesis of an infectious cDNA clone. The authors of D2 state that "mutants lacking all or part of the 3' terminal conserved region or the poly(U-UC) region were unable to infect the chimpanzee, indicating that both regions are **critical for infectivity** in vivo" (p. 2291, Abstract). The document D2 also gives the structure of the native 3' untranslated region and the different mutations realized in the study (p. 2292, Fig. 1). In the discussion, the authors of D2 mention that "conserved terminal genome sequences or structures of RNA viruses typically have a critical role for RNA replication and/or packaging" and that "although the 3' terminal 80-100 nt of different flaviviruses are heterogeneous in sequence, they all form putative stem-loop structures and have several conserved sequence elements upstream" (p. 2294, right-hand column, lines 11-16). D2 also mention that the 3' terminal sequence of 98 nucleotides identified in D2 is highly conserved among the different variants of HCV and **similar to other viruses in the Flaviviridae family** (p.2294, right-hand column, lines

21-23). Moreover, D2 states that "such sequences in the conserved region of the 3' UTR were critical for virus replication (p. 2294, right-hand column, lines 18-19).
Furthermore, D2 states that "because the poly(U-UC) region and the conserved region of the HCV 3' UTR were critical for infectivity, sequences within these regions and/or viral and host factors that interact with such sequences could represent targets for therapeutic agents against HCV" (p. 2295, left-hand column, lines 26-31).

The IPEA is the opinion that, knowing :

- from D2 : the importance of the 3' untranslated region of HCV in the infectivity of said virus, the sequence and the secondary structure of said 3' untranslated sequence and the existence of this kind of sequence in several **flaviviruses**.
- from D3 : the fact that the GBV-B virus, which is responsible for hepatitis in tamarins, belongs to the **Flaviviridae** family and is **closely related** to the human pathogen **hepatitis C virus** (p. 4985, Abstract).
- from D4 : the fact that, contrary to what was previously thought, the HCV genome RNA doesn't terminate with homopolymer tracts of either poly(U) or poly(A) but additionally comprise a 3'-terminal sequence forming a stable loop structure which is likely to be required for authentic HCV replication and recovery of infectious RNA from cDNA and a method to identify the 3' untranslated sequence of the HCV genome RNA.
- from D1 : the complete sequence of the GBV-B genome RNA lacking the 3' terminal region disclosed in the present application and the corresponding protein sequences (example 9 and more especially pp. 91-92; SEQ ID NO:393 (nucleic acid sequence), SEQ ID NO:396 and SEQ ID NO:397 (protein sequences)).

the skilled person would probably have contemplated trying to identify such a 3' -terminal region in the well-known GBV-B genome, using a well-known method like for example the method disclosed in D3.

Therefore, the subject-matter of claims 1-6, 13-14 and 17-18 can not be considered as inventive in the sense of article 33(3) PCT.

The transfection of a well-known host cell with a non inventive DNA construct comprising a nucleic acid molecule encoding a GB virus-B and the production of GB virus-B by said cells can not be considered as inventive. Therefore, claims 7-8 and 15-16 lack inventive step in the sense of article 33(3) PCT.

4.2 The subject-matter of claims 19-38 has never been disclosed or suggested in the documents cited in the ISR. Therefore, claims 19-38 are considered as inventive in the sense of article 33(3) PCT.

Re Item VIII
Certain observations on the international application

Lack of clarity; article 6 PCT.

1. In claim 1 of the present application, the isolated nucleic acid molecule is not characterized by any technical features but only by the facts that it "encodes GB virus-B" and that it is "capable of expressing said virus when transfected into cells", i.e. by the result to be achieved by said isolated nucleic acid molecule. According to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.7 : "The area defined by the claims must be as precise as the invention allows. As a general rule, claims which attempt to define the invention, or a feature thereof, by a result to be achieved should be objected to".
   The IPEA considers that the isolated nucleic acid molecule of claim 1 could be better defined by reference to specific nucleic acid sequences.

2. Claim 4 refers to a "DNA construct" comprising a nucleic acid molecule according to claim 1. The attention of the applicant is drawn to the fact that, in the present application, there is no definition of what a "DNA construct" should exactly be what renders the scope of claim 4 unclear.
   This remark also applies to claims 5 and 33.

3. Claim 9 refers to a GB virus-B polypeptide produced by the cell of claim 7. This claim is considered as a claim for a "product defined in terms of process of manufacture" by the EPO. For the EPO, this kind of claim is "admissible only if the products as such fulfil the requirements for patentability, i.e. inter alia that they are new and inventive" (Guidelines for examination in the European Patent Office, chapter C-III 4.7b).
   This remark also applies to claims 10-12.

4. Claim 24 of the present application lacks clarity for the following reasons :
   (i) Claim 24 of the present application refers to the "non-structural region of the genome of a GB virus-B" and the "non-structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".
   (ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 24. Therefore, the IPEA considers that the subject-matter of claim 24 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).
   These remarks also apply to claims 25 and 37-38.

5. Claim 27 lacks clarity for the following reasons :
   (i) Claim 27 of the present application refers to the "structural region of the genome of a GB virus-B" and the "structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".

(ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 27. Therefore, the IPEA considers that the subject-matter of claim 27 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).

These remarks also apply to claim 28.

6. Claims 36 (as far as the 5'UTR sequence is concerned) and 37-38 refer to chimeric virus genomes derived from the hepatitis C virus genome which will probably not be able to infect tamarins. Thus, claims 36 (partially) and 37-38 do not solve the same problem as the other claims of the present application, i.e. the provision of GB virus-B genome or chimeric virus genome derived from the GB virus-B genome **capable of infecting tamarins**.
Therefore, the IPEA considers that the present application lacks unity and that claims 36 (partially) and 37-38 represent an independent invention.

Lack of support (article 5 PCT in combination with article 6 PCT).

As a general remark, the attention of the applicant is drawn to the following facts :
- In the present application, there are no specific examples of nucleic acid molecules according to claims 19-32 and 36-38. Therefore, the subject-matter of claims 19-32 and 36-38 are considered as not supported by the description of the present application.
- Moreover, there is no proof at all that the chimeric nucleic acid molecules of claims 19-32 and 36 will be able to infect tamarins and, even if capable of infecting tamarins, that chimeric nucleic acid molecules will be useful for the molecular study of HCV in tamarins.

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
PC[redacted]S 00/15293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C07K14/18 C12Q1/68 C12N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17) page 4, line 18 -page 6, line 17 page 55, line 24 -page 56, line 19 page 76; example 5 page 89, line 18 -page 96 page 109; example 15 page 148; example 21 page 427, line 17 -page 432 claims --- -/--	1,2,4-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SCARSELLI ELISA ET AL: "GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity." JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, XP002150190 ISSN: 0022-538X cited in the application the whole document	19,24-26
A	HONDA MASAO ET AL: "A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, XP002150191 ISSN: 0022-538X cited in the application the whole document	19,22,23
A	YANAGI MASAYUKI ET AL: "In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, XP002150192 ISSN: 0027-8424 cited in the application	
A	YANAGI M ET AL: "Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious in vivo" VIROLOGY, vol. 244, no. 1, 1998, pages 161-172, XP002089701 ISSN: 0042-6822 cited in the application	
P,X	BUKH JENS ET AL: "Toward a surrogate model for hepatitis C virus: An infectious molecular clone of the GB virus-B hepatitis agent." VIROLOGY, vol. 262, no. 2, 30 September 1999 (1999-09-30), pages 470-478, XP002150193 ISSN: 0042-6822 the whole document	1-16,19

-/--

1

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/15293

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	SBARDELLATI ANDREA ET AL: "Identification of a novel sequence at the 3' end of the GB virus B genome." JOURNAL OF VIROLOGY, vol. 73, no. 12, December 1999 (1999-12), pages 10546-10550, XP002150194 ISSN: 0022-538X the whole document	1-16,19
P,X	BUTKIEWICZ N. ET AL.: "Virus-specific cofactor requirement and chimeric hepatitis C virus/GB virus B nonstructural protein 3." J VIROL 2000 MAY;74(9):4291-301, XP002150195 the whole document	19, 24-26, 33-35, 37,39

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted] on patent family members

Internat[redacted]l Application No
PC[redacted] 00/15293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521922 A	17-08-1995	CA 2166313 A	17-08-1995
		EP 0745129 A	04-12-1996
		JP 10337193 A	22-12-1998
		JP 9511137 T	11-11-1997
		US 5981172 A	09-11-1999
		US 5843450 A	01-12-1998
		US 6051374 A	18-04-2000
		WO 9829747 A	09-07-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 April 2001 (09.04.01)	
International application No. PCT/US00/15293	**Applicant's or agent's file reference** 2026-4308PC
International filing date (day/month/year) 02 June 2000 (02.06.00)	**Priority date** (day/month/year) 04 June 1999 (04.06.99)
Applicant BUKH, Jens et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 January 2001 (02.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Henrik Nyberg
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
2026-4308PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 15293	02/06/2000	04/06/1999
Applicant		
THE GOVERNMENT OF THE U.S.A. ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 4

   [ ] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [X] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/15293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C07K14/18 C12Q1/68 C12N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17) page 4, line 18 -page 6, line 17 page 55, line 24 -page 56, line 19 page 76; example 5 page 89, line 18 -page 96 page 109; example 15 page 148; example 21 page 427, line 17 -page 432 claims --- -/--	1,2,4-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Andres, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SCARSELLI ELISA ET AL: "GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity." JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, XP002150190 ISSN: 0022-538X cited in the application the whole document ---	19,24-26
A	HONDA MASAO ET AL: "A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, XP002150191 ISSN: 0022-538X cited in the application the whole document ---	19,22,23
A	YANAGI MASAYUKI ET AL: "In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, XP002150192 ISSN: 0027-8424 cited in the application ---	
A	YANAGI M ET AL: "Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious in vivo" VIROLOGY, vol. 244, no. 1, 1998, pages 161-172, XP002089701 ISSN: 0042-6822 cited in the application ---	
P,X	BUKH JENS ET AL: "Toward a surrogate model for hepatitis C virus: An infectious molecular clone of the GB virus-B hepatitis agent." VIROLOGY, vol. 262, no. 2, 30 September 1999 (1999-09-30), pages 470-478, XP002150193 ISSN: 0042-6822 the whole document --- -/--	1-16,19

1

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/15293

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	SBARDELLATI ANDREA ET AL: "Identification of a novel sequence at the 3' end of the GB virus B genome." JOURNAL OF VIROLOGY, vol. 73, no. 12, December 1999 (1999-12), pages 10546-10550, XP002150194 ISSN: 0022-538X the whole document ---	1-16,19
P,X	BUTKIEWICZ N. ET AL.: "Virus-specific cofactor requirement and chimeric hepatitis C virus/GB virus B nonstructural protein 3." J VIROL 2000 MAY;74(9):4291-301, XP002150195 the whole document -----	19, 24-26, 33-35, 37,39

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/15293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521922 A	17-08-1995	CA 2166313 A	17-08-1995
		EP 0745129 A	04-12-1996
		JP 10337193 A	22-12-1998
		JP 9511137 T	11-11-1997
		US 5981172 A	09-11-1999
		US 5843450 A	01-12-1998
		US 6051374 A	18-04-2000
		WO 9829747 A	09-07-1998

PATENT COOPERATION T EATY

2026 - 4308 PC
Muller

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FEILER, William
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	20.04.2001
Applicant's or agent's file reference: 2026-4308PC	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15293	02/06/2000	04/06/1999

International Patent Classification (IPC) or both national classification and IPC

C12N15/51

Applicant

THE GOVERNMENT OF THE U.S.A. ...

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04/10/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Mundel, C

Formalities officer (incl. extension of time limits)
Emslander, S
Telephone No. +49 89 2399 8718

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-31 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

CASE 2026-4308 ATTY KAM.
DUE July 20, 2001
1 mo. call-up June 20, 2001
BY J.M

Sequence listing part of the description, pages:

1-35, filed with the letter of 07.07.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-2, 4, 6-13 and 15-17 (NO) and 3, 5, 14, 18 (see Citations and explanations)
Inventive step (IS)	Claims	1-18 (NO)
Industrial applicability (IA)	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the

claims are fully supported by the description, are made:
se separate sheet

R Item II
Priority

The priority document of the present application was not available at the time where this preliminary opinion has been drafted. The present analysis is based on the hypothesis that all the claims have a priority right corresponding to the date of filing of the priority document (04.06.99).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application refers to an isolated nucleic acid molecule encoding an infectious GB virus-B, to cells transfected with said nucleic acid, to GB virus-B polypeptides and to GB virus-B. The application also refers to methods for producing GB virus-B and to compositions comprising an isolated nucleic acid molecule encoding an infectious GB virus-B. The application also refers to chimeric virus genomes comprising GB virus-B nucleic sequences and hepatitis C virus sequences, to viruses comprising such genomes and to polypeptide encoded by said chimeric virus genomes.

2. **Reference is made to the following documents :**

   D1: WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17).

   D2: YANAGI MASAYUKI ET AL: 'In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, cited in the application.

   D3: SCARSELLI ELISA ET AL: 'GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity.' JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, cited in the application.

   D4: KOLYKHALOV A. A. et al.: "Identification of a highly conserved sequence element at the 3' terminus of hepatitis C virus genome RNA". Journal of

virology, vol. 70, No. 6, June 1996, pages 3363-3371.

D5: HONDA MASAO ET AL: 'A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation.' JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, cited in the application.

The document D4 was not cited in the international search report. A copy of the document is appended hereto.

3. Lack of novelty; article 33(2) PCT.

3.1 The document D1 discloses hepatitis GB virus (HGBV) nucleic acid and amino acid sequences useful for a variety of diagnostic and therapeutic applications (Abstract). D1 claims a recombinant polynucleotide characterized by a positive stranded RNA genome wherein said genome comprises an open reading frame encoding a polyprotein having at least 35% identity and more preferably 80% identity to an amino acid sequence selected from the group consisting of HGBV-A, HGBV-B and HGBV-C (p. 4, lines 19-27). Moreover D1 refers to a **recombinant vector comprising said polynucleotide** and to **host cells** transformed with said vector (p. 5, lines 1-4). Cell which will be suitable for culturing HGBV are also disclosed (p. 55, line 25 to p. 56, line 19). Example 9 of D1 discloses the "complete" sequence of the HGBV-B genome (SEQ ID NO:393) and the corresponding amino acid sequence (SEQ ID NO: 396 and 397).

The IPEA considers that the nucleic acid sequence disclosed in SEQ ID NO:393 can be considered as encoding a GB virus-B and that said nucleic acid would be capable of expressing said virus when transfected into cells. Moreover, said nucleic acid molecule can be considered as encoding the amino acid sequence of SEQ ID NO:2. Therefore, claim 1-2, 4, 6-13 and 15-17 can not be considered as novel in the sense of article 33(2) PCT.

Moreover, the attention of the applicant is drawn to the fact that even if the 3' sequence disclosed in the present application has not been disclosed in D1,

at least some of the HGBV-B viruses used in D1 - being infectious - had said 3' terminal sequence. Therefore, even the novelty of claims 3, 5, 14 and 18 is questionable.

3.2 Claims 39 and 40 of the present application refer to a polypeptide encoded by the nucleic acid molecule of claims 19, 24 or 27. The attention of the applicant is drawn to the fact that the sequence of the polyprotein encoded by the GB virus-B was well-known from the document D1. Moreover, the scope of claims 39 and 40 also encompasses well-known hepatitis C virus proteins. Therefore, claims 39 and 40 lack novelty in the sense of article 33(2) PCT.

4. Lack of inventive step; article 33(3) PCT.

4.1 The document D2 has been considered as the most relevant document for the evaluation of the inventiveness of the claims.
D2 discloses the in vivo analysis of the **3' untranslated region of the hepatitis C virus** after in vitro mutagenesis of an infectious cDNA clone. The authors of D2 state that "mutants lacking all or part of the 3' terminal conserved region or the poly(U-UC) region were unable to infect the chimpanzee, indicating that both regions are **critical for infectivity** in vivo" (p. 2291, Abstract). The document D2 also gives the structure of the native 3' untranslated region and the different mutations realized in the study (p. 2292, Fig. 1). In the discussion, the authors of D2 mention that "conserved terminal genome sequences or structures of RNA viruses typically have a critical role for RNA replication and/or packaging" and that "although the 3' terminal 80-100 nt of different flaviviruses are heterogeneous in sequence, they all form putative stem-loop structures and have several conserved sequence elements upstream" (p. 2294, right-hand column, lines 11-16). D2 also mention that the 3' terminal sequence of 98 nucleotides identified in D2 is highly conserved among the different variant variants of HCV and **similar to other viruses in the Flaviviridae family** (p.2294, right-hand column, lines 21-23). Moreover, D2 states that "such sequences in the conserved region of the 3' UTR were critical for virus replication (p. 2294, right-hand

column, lines 18-19).
Furthermore, D2 states that "because the poly(U-UC) region and the conserved region of the HCV 3' UTR were critical for infectivity, sequences within these regions and/or viral and host factors that interact with such sequences could represent targets for therapeutic agents against HCV" (p. 2295, left-hand column, lines 26-31).

The IPEA is the opinion that, knowing :

- from D2 : the importance of the 3' untranslated region of HCV in the infectivity of said virus, the sequence and the secondary structure of said 3' untranslated sequence and the existence of this kind of sequence in several **flaviviruses**.
- from D3 : the fact that the GBV-B virus, which is responsible for hepatitis in tamarins, belongs to the **Flaviviridae** family and is **closely related** to the human pathogen **hepatitis C virus** (p. 4985, Abstract).
- from D4 : the fact that, contrary to what was previously thought, the HCV genome RNA doesn't terminate with homopolymer tracts of either poly(U) or poly(A) but additionally comprise a 3'-terminal sequence forming a stable loop structure which is likely to be required for authentic HCV replication and recovery of infectious RNA from cDNA and a method to identify the 3' untranslated sequence of the HCV genome RNA.
- from D1 : the complete sequence of the GBV-B genome RNA lacking the 3' terminal region disclosed in the present application and the corresponding protein sequences (example 9 and more especially pp. 91-92; SEQ ID NO:393 (nucleic acid sequence), SEQ ID NO:396 and SEQ ID NO:397 (protein sequences)).

the skilled person would probably have contemplated trying to identify such a 3' -terminal region in the well-known GBV-B genome, using a well-known method like for example the method disclosed in D3.

Therefore, the subject-matter of claims 1-6, 13-14 and 17-18 can not be considered as inventive in the sense of article 33(3) PCT.

The transfection of a well-known host cell with a non inventive DNA construct

comprising a nucleic acid molecule encoding a GB virus-B and the production of GB virus-B by said cells can not be considered as inventive. Therefore, claims 7-8 and 15-16 lack inventive step in the sense of article 33(3) PCT.

Re Item VIII
Certain observations on the international application

Lack of clarity; article 6 PCT.

1. In claim 1 of the present application, the isolated nucleic acid molecule is not characterized by any technical features but only by the facts that it "encodes GB virus-B" and that it is "capable of expressing said virus when transfected into cells", i.e. by the result to be achieved by said isolated nucleic acid molecule. According to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.7 : "The area defined by the claims must be as precise as the invention allows. As a general rule, claims which attempt to define the invention, or a feature thereof, by a result to be achieved should be objected to".
   The IPEA is the opinion that the isolated nucleic acid molecule of claim 1 could be better defined by reference to specific nucleic acid sequences.

2. Claim 4 refers to a "DNA construct" comprising a nucleic acid molecule according to claim 1. The attention of the applicant is drawn to the fact that, in the present application, there is no definition of what a "DNA construct" should exactly be what renders the scope of claim 4 unclear.
   This remark also applies to claims 5 and 33.

3. Claim 9 refers to a GB virus-B polypeptide produced by the cell of claim 7. This claim is considered as a claim for a "product defined in terms of process of manufacture" by the EPO. For the EPO, this kind of claim is "admissible only if the products as such fulfil the requirements for patentability, i.e. inter alia that they are new and inventive" (Guidelines for examination in the European Patent Office, chapter C-III 4.7b).
   This remark also applies to claims 10-12.

4. Claim 24 of the present application lacks clarity for the following reasons :
   (i) Claim 24 of the present application refers to the "non-structural region of the genome of a GB virus-B" and the "non-structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".
   (ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 24. Therefore, the IPEA is the opinion that the subject-matter of claim 24 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).

   These remarks also apply to claims 25 and 37-38.

5. Claim 27 lacks clarity for the following reasons :
   (i) Claim 27 of the present application refers to the "structural region of the genome of a GB virus-B" and the "structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".
   (ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 27. Therefore, the IPEA is the opinion that the subject-matter of claim 27 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).

   These remarks also apply to claim 28.

6. Claims 36 (as far as the 5'UTR sequence is concerned) and 37-38 refer to chimeric virus genomes derived from the hepatitis C virus genome which will probably not be able to infect tamarins. Thus, claims 36 (partially) and 37-38 do not solve the same problem as the other claims of the present application, i.e. the provision of GB virus-B genome or chimeric virus genome derived from the GB virus-B genome **capable of infecting tamarins**.
Therefore, the IPEA is the opinion that the present application lacks unity and that claims 36 (partially) and 37-38 represent an independent invention.

Lack of support (article 5 PCT in combination with article 6 PCT).

As a general remark, the attention of the applicant is drawn to the following facts :
- In the present application, there are no specific examples of nucleic acid molecules according to claims 19-32 and 36-38. Therefore, the subject-matter of claims 19-32 and 36-38 could be considered as not supported by the description of the present application.
- Moreover, there is no proof at all that the chimeric nucleic acid molecules of claims 19-32 and 36 will be able to infect tamarins and, even if capable of infecting tamarins, that chimeric nucleic acid molecules will be useful for the molecular study of HCV in tamarins.

PATENT COOPERATION TREATY

2026-4308PC
Lombillo

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FEILER, William
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24.08.2001
Applicant's or agent's file reference 2026-4308PC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15293	02/06/2000	04/06/1999

Applicant
THE GOVERNMENT OF THE U.S.A. ...

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hingel, W Tel.+49 89 2399-8717

Form PCT/IPEA/416 (July 1992)

TENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2026-4308PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15293	02/06/2000	04/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/51		
Applicant THE GOVERNMENT OF THE U.S.A. ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/01/2001	24.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mundel, C Telephone No. +49 89 2399 7314

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/15293

I. Basis of the rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*: .
Description, pages:

1-31 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-35, filed with the letter of 07.07.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-38
	No:	Claims	1-2, 4, 6-13, 15-17 and 39-40 & 3, 5, 14, 18 (see Citations and explanations)
Inventive step (IS)	Yes:	Claims	19-38
	No:	Claims	1-18 and 39-40
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II
Priority

The priority document of the present application was not available at the time where thisInternational Preliminary Examination Report (IPER) has been drafted. The present analysis is based on the hypothesis that all the claims have a priority right corresponding to the date of filing of the priority document (04.06.99).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application refers to an isolated nucleic acid molecule encoding an infectious GB virus-B, to cells transfected with said nucleic acid, to GB virus-B polypeptides and to GB virus-B. The application also refers to methods for producing GB virus-B and to compositions comprising an isolated nucleic acid molecule encoding an infectious GB virus-B. The application also refers to chimeric virus genomes comprising GB virus-B nucleic sequences and hepatitis C virus sequences, to viruses comprising such genomes and to polypeptide encoded by said chimeric virus genomes.

2. **Reference is made to the following documents :**

   D1: WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17).

   D2: YANAGI MASAYUKI ET AL: 'In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, cited in the application.

   D3: SCARSELLI ELISA ET AL: 'GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity.' JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, cited in the application.

   D4: KOLYKHALOV A. A. et al.: "Identification of a highly conserved sequence element at the 3' terminus of hepatitis C virus genome RNA". Journal of

virology, vol. 70, No. 6, June 1996, pages 3363-3371.

D5: HONDA MASAO ET AL: 'A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation.' JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, cited in the application.

The document D4 was not cited in the international search report.

3. Lack of novelty; article 33(2) PCT.

3.1 The document D1 discloses hepatitis GB virus (HGBV) nucleic acid and amino acid sequences useful for a variety of diagnostic and therapeutic applications (Abstract). D1 claims a recombinant polynucleotide characterized by a positive stranded RNA genome wherein said genome comprises an open reading frame encoding a polyprotein having at least 35% identity and more preferably 80% identity to an amino acid sequence selected from the group consisting of HGBV-A, HGBV-B and HGBV-C (p. 4, lines 19-27). Moreover D1 refers to a **recombinant vector comprising said polynucleotide** and to **host cells** transformed with said vector (p. 5, lines 1-4). Cells which will be suitable for culturing HGBV are also disclosed (p. 55, line 25 to p. 56, line 19). Example 9 of D1 discloses the "complete" sequence of the HGBV-B genome (SEQ ID NO:393) and the corresponding amino acid sequence (SEQ ID NO: 396 and 397).

The IPEA considers that the nucleic acid sequence disclosed in SEQ ID NO:393 can be considered as encoding a GB virus-B and that said nucleic acid would be capable of expressing said virus when transfected into cells. Moreover, said nucleic acid molecule can be considered as encoding the amino acid sequence of SEQ ID NO:2. Therefore, claim 1-2, 4, 6-13 and 15-17 can not be considered as novel in the sense of article 33(2) PCT.

Moreover, the attention of the applicant is drawn to the fact that even if the 3' sequence disclosed in the present application has not been disclosed in D1, at least some of the HGBV-B viruses used in D1 - being infectious - had said

3' terminal sequence. Therefore, even the novelty of claims 3, 5, 14 and 18 is questionable.

3.2 Claims 39 and 40 of the present application refer to a polypeptide encoded by the nucleic acid molecule of claims 19, 24 or 27. The attention of the applicant is drawn to the fact that the sequence of the polyprotein encoded by the GB virus-B was well-known from the document D1. Moreover, the scope of claims 39 and 40 also encompasses well-known hepatitis C virus proteins. Therefore, claims 39 and 40 lack novelty in the sense of article 33(2) PCT.

3.3 The subject-matter of claims 19-38 has never been disclosed in the documents cited in the International Search Report (ISR). Therefore, claims 19-38 are considered as novel in the sense of article 33(2) PCT.

4. Lack of inventive step; article 33(3) PCT.

4.1 The document D2 has been considered as the most relevant document for the evaluation of the inventiveness of the claims.
D2 discloses the in vivo analysis of the **3' untranslated region of the hepatitis C virus** after in vitro mutagenesis of an infectious cDNA clone. The authors of D2 state that "mutants lacking all or part of the 3' terminal conserved region or the poly(U-UC) region were unable to infect the chimpanzee, indicating that both regions are **critical for infectivity** in vivo" (p. 2291, Abstract). The document D2 also gives the structure of the native 3' untranslated region and the different mutations realized in the study (p. 2292, Fig. 1). In the discussion, the authors of D2 mention that "conserved terminal genome sequences or structures of RNA viruses typically have a critical role for RNA replication and/or packaging" and that "although the 3' terminal 80-100 nt of different flaviviruses are heterogeneous in sequence, they all form putative stem-loop structures and have several conserved sequence elements upstream" (p. 2294, right-hand column, lines 11-16). D2 also mention that the 3' terminal sequence of 98 nucleotides identified in D2 is highly conserved among the different variants of HCV and **similar to other viruses in the Flaviviridae family** (p.2294, right-hand column, lines

21-23). Moreover, D2 states that "such sequences in the conserved region of the 3' UTR were critical for virus replication (p. 2294, right-hand column, lines 18-19).
Furthermore, D2 states that "because the poly(U-UC) region and the conserved region of the HCV 3' UTR were critical for infectivity, sequences within these regions and/or viral and host factors that interact with such sequences could represent targets for therapeutic agents against HCV" (p. 2295, left-hand column, lines 26-31).

The IPEA is the opinion that, knowing :

- from D2 : the importance of the 3' untranslated region of HCV in the infectivity of said virus, the sequence and the secondary structure of said 3' untranslated sequence and the existence of this kind of sequence in several **flaviviruses**.
- from D3 : the fact that the GBV-B virus, which is responsible for hepatitis in tamarins, belongs to the **Flaviviridae** family and is **closely related** to the human pathogen **hepatitis C virus** (p. 4985, Abstract).
- from D4 : the fact that, contrary to what was previously thought, the HCV genome RNA doesn't terminate with homopolymer tracts of either poly(U) or poly(A) but additionally comprise a 3'-terminal sequence forming a stable loop structure which is likely to be required for authentic HCV replication and recovery of infectious RNA from cDNA and a method to identify the 3' untranslated sequence of the HCV genome RNA.
- from D1 : the complete sequence of the GBV-B genome RNA lacking the 3' terminal region disclosed in the present application and the corresponding protein sequences (example 9 and more especially pp. 91-92; SEQ ID NO:393 (nucleic acid sequence), SEQ ID NO:396 and SEQ ID NO:397 (protein sequences)).

the skilled person would probably have contemplated trying to identify such a 3' -terminal region in the well-known GBV-B genome, using a well-known method like for example the method disclosed in D3.

Therefore, the subject-matter of claims 1-6, 13-14 and 17-18 can not be considered as inventive in the sense of article 33(3) PCT.

The transfection of a well-known host cell with a non inventive DNA construct comprising a nucleic acid molecule encoding a GB virus-B and the production of GB virus-B by said cells can not be considered as inventive. Therefore, claims 7-8 and 15-16 lack inventive step in the sense of article 33(3) PCT.

4.2 The subject-matter of claims 19-38 has never been disclosed or suggested in the documents cited in the ISR. Therefore, claims 19-38 are considered as inventive in the sense of article 33(3) PCT.

Re Item VIII
Certain observations on the international application

Lack of clarity; article 6 PCT.

1. In claim 1 of the present application, the isolated nucleic acid molecule is not characterized by any technical features but only by the facts that it "encodes GB virus-B" and that it is "capable of expressing said virus when transfected into cells", i.e. by the result to be achieved by said isolated nucleic acid molecule. According to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.7 : "The area defined by the claims must be as precise as the invention allows. As a general rule, claims which attempt to define the invention, or a feature thereof, by a result to be achieved should be objected to".
   The IPEA considers that the isolated nucleic acid molecule of claim 1 could be better defined by reference to specific nucleic acid sequences.

2. Claim 4 refers to a "DNA construct" comprising a nucleic acid molecule according to claim 1. The attention of the applicant is drawn to the fact that, in the present application, there is no definition of what a "DNA construct" should exactly be what renders the scope of claim 4 unclear.
   This remark also applies to claims 5 and 33.

3. Claim 9 refers to a GB virus-B polypeptide produced by the cell of claim 7. This claim is considered as a claim for a "product defined in terms of process of manufacture" by the EPO. For the EPO, this kind of claim is "admissible only if the products as such fulfil the requirements for patentability, i.e. inter alia that they are new and inventive" (Guidelines for examination in the European Patent Office, chapter C-III 4.7b).
   This remark also applies to claims 10-12.

4. Claim 24 of the present application lacks clarity for the following reasons :
   (i) Claim 24 of the present application refers to the "non-structural region of the genome of a GB virus-B" and the "non-structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".
   (ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 24. Therefore, the IPEA considers that the subject-matter of claim 24 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).
   These remarks also apply to claims 25 and 37-38.

5. Claim 27 lacks clarity for the following reasons :
   (i) Claim 27 of the present application refers to the "structural region of the genome of a GB virus-B" and the "structural region of a hepatitis C virus genome". The use of these wordings renders the scope of the claim unclear since there is no clear definition of what such regions should precisely be. The attention of the applicant is drawn to the fact that even if these wordings are defined in the description of the present application, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-4.2 : a claim should be drafted in such a form that its "meaning is clear from the wording of the claim alone".

(ii) The attention of the applicant is drawn to the fact that there is no example in the present application of a nucleic acid molecule according to claim 27. Therefore, the IPEA considers that the subject-matter of claim 27 can not be considered as supported by the description of the present application (article 5 PCT in combination with article 6 PCT).

These remarks also apply to claim 28.

6. Claims 36 (as far as the 5'UTR sequence is concerned) and 37-38 refer to chimeric virus genomes derived from the hepatitis C virus genome which will probably not be able to infect tamarins. Thus, claims 36 (partially) and 37-38 do not solve the same problem as the other claims of the present application, i.e. the provision of GB virus-B genome or chimeric virus genome derived from the GB virus-B genome **capable of infecting tamarins**.
Therefore, the IPEA considers that the present application lacks unity and that claims 36 (partially) and 37-38 represent an independent invention.

Lack of support (article 5 PCT in combination with article 6 PCT).

As a general remark, the attention of the applicant is drawn to the following facts :
- In the present application, there are no specific examples of nucleic acid molecules according to claims 19-32 and 36-38. Therefore, the subject-matter of claims 19-32 and 36-38 are considered as not supported by the description of the present application.
- Moreover, there is no proof at all that the chimeric nucleic acid molecules of claims 19-32 and 36 will be able to infect tamarins and, even if capable of infecting tamarins, that chimeric nucleic acid molecules will be useful for the molecular study of HCV in tamarins.

WO 00/75337
PCT/US00/15293

PATENT COOPERATION TREATY 2026-4308PC

RECEIVED Muller

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
FEILER, William, S.
Morgan & Finnegan, LLP
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

2000 DEC 28 A 8:44
MORGAN & FINNEGAN LLP

Date of mailing (day/month/year) 14 December 2000 (14.12.00)	
Applicant's or agent's file reference 2026-4308PC	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US00/15293	02 June 2000 (02.06.00)	04 June 1999 (04.06.99)

Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALT et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   14 December 2000 (14.12.00) under No. WO 00/75337

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, ch min des C l mbett s** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

2026-4308PC
KAM

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
Morgan & Finnegan, L.L.P.
Attn. FEILER, W.
345 Park Avenue
New York, New York 10154
UNITED STATES OF AMERICA

2000 NOV -3 P 2:44
FINNEGAN LLP

CASE 2026-4308PC ATTY KAM
1 Mo. Call Up December 31, 2000
DUE January 31, 2001 (U.S. Suppl. IDS)
BY J.M

Date of mailing *(day/month/year)* 31/10/2000	
Applicant's or agent's file reference 2026-4308PC	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 00/ 15293	International filing date *(day/month/year)* 02/06/2000
Applicant THE GOVERNMENT OF THE U.S.A. ...	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

2026-4308PC
CASE ATTY KAM
DUE December 31, 2000 (Art. 19 Amend. Due!)
1 mo. call-up November 30, 2000
BY J.M.

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mireille Claudepierre

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2026-4308PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 15293	02/06/2000	04/06/1999
Applicant		
THE GOVERNMENT OF THE U.S.A. ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 4

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [X] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/15293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521922 A	17-08-1995	CA 2166313 A	17-08-1995
		EP 0745129 A	04-12-1996
		JP 10337193 A	22-12-1998
		JP 9511137 T	11-11-1997
		US 5981172 A	09-11-1999
		US 5843450 A	01-12-1998
		US 6051374 A	18-04-2000
		WO 9829747 A	09-07-1998

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C07K14/18 C12Q1/68 C12N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17) page 4, line 18 -page 6, line 17 page 55, line 24 -page 56, line 19 page 76; example 5 page 89, line 18 -page 96 page 109; example 15 page 148; example 21 page 427, line 17 -page 432 claims --- -/--	1,2,4-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCARSELLI ELISA ET AL: "GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity." JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, XP002150190 ISSN: 0022-538X cited in the application the whole document	19,24-26
A	HONDA MASAO ET AL: "A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, XP002150191 ISSN: 0022-538X cited in the application the whole document	19,22,23
A	YANAGI MASAYUKI ET AL: "In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, XP002150192 ISSN: 0027-8424 cited in the application	
A	YANAGI M ET AL: "Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious in vivo" VIROLOGY, vol. 244, no. 1, 1998, pages 161-172, XP002089701 ISSN: 0042-6822 cited in the application	
P,X	BUKH JENS ET AL: "Toward a surrogate model for hepatitis C virus: An infectious molecular clone of the GB virus-B hepatitis agent." VIROLOGY, vol. 262, no. 2, 30 September 1999 (1999-09-30), pages 470-478, XP002150193 ISSN: 0042-6822 the whole document	1-16,19

-/--

1

International Application No
PCT/US 00/15293

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SBARDELLATI ANDREA ET AL: "Identification of a novel sequence at the 3' end of the GB virus B genome." JOURNAL OF VIROLOGY, vol. 73, no. 12, December 1999 (1999-12), pages 10546-10550, XP002150194 ISSN: 0022-538X the whole document ---	1-16,19
P,X	BUTKIEWICZ N. ET AL.: "Virus-specific cofactor requirement and chimeric hepatitis C virus/GB virus B nonstructural protein 3." J VIROL 2000 MAY;74(9):4291-301, XP002150195 the whole document -----	19, 24-26, 33-35, 37,39

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 2026-4308PC

Box No. I TITLE OF INVENTION

INFECTIOUS cDNA CLONE OF GB VIRUS B AND USES THEREOF

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

The Government of the United States of America
as represented by the Secretary, Department of
Health and Human Services
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard, Suite 325
Rockville, Maryland 20852
US

☐ This person is also inventor.

Telephone No. (301) 496-7056

Facsimile No. (301) 402-0220

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BUKH, Jens
2018 Baltimore Road, #J42
Rockville, Maryland 20851
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DK

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FEILER, William S.; BORK, Richard W. and CHEN, Haiyan
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
US

Telephone No. (212) 758-4800

Facsimile No. (212) 751-6849

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III [redacted]THER APPLICANT(S) AND/OR (FURTHE[redacted]VENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YANAGI, Masayuki
257 Congressional Lane, #402
Rockville, Maryland 20852
US

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

EMERSON, Suzanne U.
4517 Everett Street
Kensington, Maryland 20895
US

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PURCELL, Robert H.
17517 White Ground Road
Boyds, Maryland 20841
US

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates
- ☒ **AL** Albania
- ☒ **AM** Armenia
- ☒ **AT** Austria
- ☒ **AU** Australia
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria
- ☒ **BR** Brazil
- ☒ **BY** Belarus
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China
- ☒ **CR** Costa Rica
- ☒ **CU** Cuba
- ☒ **CZ** Czech Republic
- ☒ **DE** Germany
- ☒ **DK** Denmark
- ☒ **DM** Dominica
- ☒ **EE** Estonia
- ☒ **ES** Spain
- ☒ **FI** Finland
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada
- ☒ **GE** Georgia
- ☒ **GH** Ghana
- ☒ **GM** Gambia
- ☒ **HR** Croatia
- ☒ **HU** Hungary
- ☒ **ID** Indonesia
- ☒ **IL** Israel
- ☒ **IN** India
- ☒ **IS** Iceland
- ☒ **JP** Japan
- ☒ **KE** Kenya
- ☒ **KG** Kyrgyzstan
- ☒ **KP** Democratic People's Republic of Korea
- ☒ **KR** Republic of Korea
- ☒ **KZ** Kazakhstan
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MA** Morocco
- ☒ **MD** Republic of Moldova
- ☒ **MG** Madagascar
- ☒ **MK** The former Yugoslav Republic of Macedonia
- ☒ **MN** Mongolia
- ☒ **MW** Malawi
- ☒ **MX** Mexico
- ☒ **NO** Norway
- ☒ **NZ** New Zealand
- ☒ **PL** Poland
- ☒ **PT** Portugal
- ☒ **RO** Romania
- ☒ **RU** Russian Federation
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia
- ☒ **SK** Slovakia
- ☒ **SL** Sierra Leone
- ☒ **TJ** Tajikistan
- ☒ **TM** Turkmenistan
- ☒ **TR** Turkey
- ☒ **TT** Trinidad and Tobago
- ☒ **TZ** United Republic of Tanzania
- ☒ **UA** Ukraine
- ☒ **UG** Uganda
- ☒ **US** United States of America
  continuation
- ☒ **UZ** Uzbekistan
- ☒ **VN** Viet Nam
- ☒ **YU** Yugoslavia
- ☒ **ZA** South Africa
- ☒ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ DZ People's Repbulic of Algeria
- ☒ AG Antigua and Barbuda
- [x] MZ Mozambique

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit)*

Box No. VI PRIORITY CL[redacted] ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application receiving Office
item (1) 04 June 1999 (04.06.99)	60/137,694	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*: Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	5
description (excluding sequence listing part)	:	31
claims	:	5
abstract	:	1
drawings	:	21
sequence listing part of description	:	35
Total number of sheets	:	98

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet (in duplicate)
2. ☒ separate signed power of attorney (Unsigned)
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☒ nucleotide and/or amino acid sequence listing in computer readable form Statement under 37 CFR &1.821(f) and WIPO
9. ☒ other *(specify)*: Standard ST. 25; Transmittal Letter

Figure of the drawings which should accompany the abstract: Fig. 1

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

William S. Feiler
Agent for Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. V - Designation of States

US United States of America - Continuation of US Provisional Application Serial No. 60/137,694, filed 04 June 1999 (04.06.99)

This sheet ... ...ot part of and does not count as a sheet of the ...ernational application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 2026-4308PC

Applicant: The Government of the United States of America as represented by the Secretary, Department of Health and Human Services, et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . $ 240.00 [T]

2. SEARCH FEE . . . . . $ 990.00 [S]

International search to be carried out by EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 98 sheets.

first 30 sheets . . . . . $ 427.00 [b1]

68 remaining sheets x $ 10.00 additional amount = $ 680.00 [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . $1,107.00 [B]

Designation Fees

The international application contains 85 designations.

8 number of designation fees payable *(maximum 8)* x $92.00 amount of designation fee = $ 736.00 [D]

Add amounts entered at B and D and enter total at I . . . . . $1,843.00 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . $ 15.00 [P]

5. TOTAL FEES PAYABLE . . . . . $3,088.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☒ cheque	☐ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ US

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

13-4500 — Deposit Account No.

02 June 2000 — Date *(day/month/year)*

William S. Feiler — Signature William S. Feiler